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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/127,624	08/03/98	PONCE DE LEON	F 002076-007

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ART UNIT	**PAPER NUMBER**
1633	4

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/127,624	Ponce De Leon et al.
Examiner	**Group Art Unit**
Deborah Clark	1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Objections

1. The numbering of claims is not accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 16-20 have been renumbered 17-21. It is noted that claim 16 was duplicated and appeared at the bottom of page 34 and at the top of page 35. The second recitation of claim 16 has been numbered claim 17 and the remaining claims renumbered 18-21.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 14-17 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. Claims 14-17 are directed to a method of making a chimeric avian which requires use of transfected PGCs. Claims 19-21 are directed to a PGC cell line.

The instant specification does not enable making of a chimeric avian where the chimeric avian expresses a polypeptide that was inserted by way of using a PGC which was transfected with a nucleic acid encoding said polypeptide. The nature of the claimed invention is making a transgenic chimeric avian. The state of the art is not well established because the success in making transgenic birds has been limited as acknowledged by applicants (see pages 3-5). The specification does not provide specific guidance as to how to design a construct for use in producing transgenic avians, instead the specification relies upon the art to provide such. However, though the art supplies the physical/mechanical means for producing chimeric avians, the production of transgenic birds which have the desired phenotype remains unpredictable (see Simkiss at page 130, last two ¶'s, and Sang, the section entitled 'Novel products...' bridging pages 418-419). The specification does not provide any working example which demonstrates the production of a chimeric bird where the PGCs were transfected with a nucleic acid. In fact, applicants tried and were unsuccessful in stably maintaining transfected PGCs. The PGCs were transiently transfected with a marker gene for the purpose of maintaining a selectable phenotype (see page 30). Applicants reported that only 1/50 PGCs were transfected and could not be stably maintained. Therefore, it is not clear that the gene would be expressed in a transgenic bird because the transfection was transient. It is likely that a construct for successful transfection for the purpose of making a transgenic bird would require a large amount of experimentation.

The instant specification does not enable one of skill in the art to make or use a PGC cell line. The nature of the claimed invention is a cell line. By definition a cell line is made up of immortalized cells (see Molecular Biology of the Cell, page 162). The state of the art of making cell lines is well established. However, there was no success in making a PGC cell line at the time of the invention. Applicants have demonstrated the maintaining of PGCs for up to four months and point to two cell cultures which were cryopreserved. However, one of the cell lines were reported as having neuronal cell morphology. Further, applicants disclose that at four months the cultures appear to *comprise* PGCs (see page 29 lines 12-13). This statement leads one to expect that some cells in the culture are differentiating. Further, the description of long term cultures (see section beginning on page 28) sounds as though the cells are differentiating, aging, and the appearance is changing. Therefore, these cells do not seem to be immortalized. This would not fit within the definition of a cell line. Therefore, one of skill in the art has not been enabled to make or use a cell line of PGCs. The making of a true PGC cell line would require a large amount of further experimentation.

In conclusion, given the nature of the invention as described above, the state of the arts, the level of predictability found in the arts, the guidance set forth in the specification, the working examples set forth in the specification, and the amount of experimentation deemed necessary to practice the claimed invention, one of skill in the art would have to perform undue experimentation to practice the claimed invention.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "prolonged periods" in claim 1 is a relative term which renders the claim indefinite. The phrase "prolonged periods" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 10, 15, 16, and 17 recite the phrase "therapeutic polypeptide". It is not clear what a therapeutic polypeptide is. Is the polypeptide therapeutic to the resultant chicken, someone ingesting an egg, or the developing embryo, or, a polypeptide which is to be produced by the chicken or egg which is then to be used as a pharmaceutical composition, etc.? The specification does not define what is meant by therapeutic polypeptide. It is not clear how the skilled artisan is to ascertain what is encompassed by the claims. Therefore, the claims are indefinite.

Claim 11 recites "the desired PGC phenotype", however, there is no antecedent basis for this recitation found elsewhere in the claim. Further, it is not clear what is meant by "the desired PGC phenotype". As indicated by applicants certain markers of PGCs are not well defined and are controversial. Therefore, it is not clear how the skilled artisan is to be apprised as to the scope of the claims.

Claims not specifically discussed above are rejected due to their dependency upon one or more of the rejected claims.

Double Patenting

6. Applicant is advised that should claim 16 be found allowable, claim 17 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-6, 11-13, and 18 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 11-13, and 17 of copending Application No. 08/905,773. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims herein encompass the claims of '773.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-13, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pain et al.

Claims 1-10 are directed a method of culturing PGCs. Claims 11-13 and 18 are directed to a method of producing chimeric avians.

Pain et al. teach the culturing of chicken embryonic cells in medium comprising 10 ng/ml bFGF, 20 ng/ml IGF, 1% vol/vol SCF, and 1% vol/vol LIF (see page 2340, ¶1). The cells were able to differentiate *in vitro* into four lineages and were shown to provide germ-line transmission (see page 2344, column 2). The cells were cultured in an undifferentiated state for more than 160 days (see page 2345, column 2). Pain et al. do not refer to the cells as PGCs, but rather as potential Embryonic Stem cells (ES cells). However, Pain et al. do not show that the cell were pluripotent. The cells share characteristics with PGCs and were obtained from the donor embryos at stage X. It is known that PGCs are present in the epiblast at stage X. Therefore, it is likely, as

admitted by applicants (see pages 6-7 of the specification) that the culture at least contained PGCs. In addition, even if the cells described by Pain et al. were not PGCs, given the similar characteristics and the similar stage of derivation, one would expect similar culture conditions to maintain PGCs. In regards to claim 3, while the concentration of growth factors and cytokines as used by Pain et al. are approximately 1000X applicant's minimal values, it is well within the skill of the artisan to manipulate these concentrations to optimize the culture conditions. Claim 18 specifies that the PGCs were injected into the recipient via the dorsal aorta or marginal vein. Pain et al. injected the PGCs into the subgerminal cavity. However, the mechanics of transfer was well known at the time of invention and the location of the introduction of donor cells would be routinely optimized by the skilled artisan.

Pain et al. do not demonstrate the addition of nucleic acid to the PGCs. However, Pain et al. discusses the similarity of the proposed cells with that of murine embryonic stem cells and discusses method used up to that time for production of an animal with a modified genome (see page 2339). The level of skill in the art of molecular biology is very high such that one of skill in the art would know how to transform PGCs and would readily expect success in doing so. Therefore, one would be motivated to transfect the PGCs with a marker gene or another gene in order to confirm the presence of the PGCs in a resulting bird.

Therefore, it would have been *prima facie* obvious to one of skill in the art at the time the invention was made to culture PGCs using LIF, SCF, bFGF, and IGF, and to use the cells to make chimeric avians.

Conclusion

11. No claim is allowed.

12. Claims 14-17, and 19-21 are free of the prior art of record. The prior art did not teach a method of making chimeric avians where the chimeric avians were transgenic due to transfection of PGCs. Though one of skill in the art would readily know how to transfect PGCs, obtaining a transgenic bird is unpredictable and one would not reasonably expect success in doing so. The prior art did not teach a PGC cell line and given the difficulty in producing a PGC cell line one would not reasonably expect success in doing so.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Clark whose telephone number is (703) 305-4051. The examiner can normally be reached on Mondays-Fridays from 7:10 a.m. EST to 3:40 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Deborah Clark

DEBORAH J. CLARK
PATENT EXAMINER